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Teicoplanin therapy for *Staphylococcus aureus* septicaemia: relationship between pre-dose serum concentrations and outcome

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Logistic regression analysis was performed on data drawn from a clinical trials database for *Staphylococcus aureus* septicaemia treated with teicoplanin. Variables analysed were age, body weight, mean pre-dose and post-dose serum teicoplanin concentrations, mean dose (mg or mg/kg body weight) and combination versus monotherapy. Only two variables correlated with clinical outcome at a significance level better than 0.05: age ($P = 0.012$) and mean pre-dose serum concentration ($P = 0.010$). The probability of successful treatment declined with age and increased with mean pre-dose serum concentration.

Introduction

During early development, the pharmacokinetics of new systemic antimicrobials is studied in healthy volunteers, the well elderly and in uninfected patients with stable organ impairment, such as varying degrees of renal impairment or liver disease.[1] In phase III or IV studies, pharmacokinetics studies are conducted typically in patients with proven or suspected infection and those undergoing surgery or rapidly changing organ function.[2–4] Such studies rarely integrate pharmacokinetic and susceptibility data to derive pharmacodynamic parameters that can be linked to treatment outcome. However, such an approach is both relevant and possible.[5,6] The lack of correlation between pharmacokinetics in healthy volunteers and efficacy in clinical trials, and the lack of understanding of the precise pharmacodynamic determinants of outcome cause difficulties in deciding dosage and therapeutic monitoring, especially when routine measurement of serum concentrations may form part of patient management. All of these problems have been encountered with the glycopeptides teicoplanin and vancomycin,[7–10] although available evidence suggests that the duration of antimicrobial concentrations over the MIC for the potential pathogens is an important pharmacodynamic parameter for these antimicrobials.[11,12]

In our review of six published clinical studies in which teicoplanin serum concentrations were measured, it appeared that both serum teicoplanin concentrations and teicoplanin concentration/MIC ratios were related to clinical success.[13] However, crucial information was often lacking in the published form of these studies. In our analysis, we have drawn on an extensive teicoplanin clinical trial database to establish by logistic regression what relationship, if any, exists between clinical outcome and factors such as patient demographics, dosage regimen, serum concentration and teicoplanin MIC for the infecting organism.

Materials and methods

Rationale

To establish which factors account for treatment success, the study population required a reasonable percentage of failures, and so descriptive statistics from the entire database were examined to determine the main 'failure' groups present. The study database, held by Hoechst Marion Roussel (Bridgwater, NJ, USA) contained detailed information about 719 patients from a variety of studies who had been treated with teicoplanin.

The organism that accounted for the most failures was *Staphylococcus aureus*, with 42 (12.1%) failures from a total group of 348 patients. *S. aureus* was also the most frequent single organism, and although the percentage of failures was similar to those for some other species or groups (e.g. 13.0% for coagulase-negative staphylococci), no other species or group had sufficient numbers to form a 'clean' group for more detailed analysis. Although severity of infection was not available on the database, site of infec-

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tion was always recorded. When these data were tabulated it became clear that patients with *S. aureus* in blood cultures formed one of the largest groups, and also contained a substantial number of failures.

It was decided therefore to focus on patients who had *S. aureus* single organism infections and for whom the site of infection was recorded as septicaemia. Also, *S. aureus* is the most challenging pathogen for any antibiotic with Gram-positive activity, given its ability to cause infection in a wide range of patients either in the community or in hospital.

Patients

Ninety-two patients had been treated for septicaemia caused by *S. aureus* as a single infection, and of these, 80 patients had either been cured or had failed treatment. These 80 patients formed the basis of our analysis, with 78 being included in the final logistic regression model.

The remaining 12 patients, who had 'improved', were also considered. However, preliminary analyses in which these patients were combined with either 'cured' or 'failed' groups made no difference to either model and so they were excluded from further analysis.

Teicoplanin dosing

Drug dosing information included dates and quantity of every drug administration. Where the same dose had been given for several days data were entered into the database as a single record of the dose together with the start and stop dates. Where different doses were given on the same day each dose was recorded. Using these data a computer program was written to calculate duration of treatment, mean dose administered, cumulative dose and dose in mg/kg body weight, where body weight was recorded.

Mean dose was generally calculated by taking total dose and dividing by the number of days from start to finish of therapy. However, because one patient had not been treated continuously, a second mean dose (and a second mean mg/kg body weight) was calculated in which the denominator was the number of days on which treatment was actually administered. Both types of mean were included in analyses.

Serum teicoplanin concentrations

Serum concentrations of teicoplanin were recorded before commencing drug infusion (pre-dose concentration) and approximately 1 h after the infusion had been completed (post-dose concentration). Patients did not all have the same number of pre- or post-dose estimations; also, the days on which measurements were taken varied from patient to patient. Thus, although serum concentrations have been analysed day by day over the study period, it must be borne in mind that it is not the same patients who are being measured on each day.

Preliminary analysis of the serum concentration data suggested that there was greater consistency in the pre-dose data than in the post-dose data. One obvious explanation for this is that the time of the pre-dose can be defined precisely, whereas the post-dose is often less precise. As it was also considered from previous experience that pre-dose concentrations were more important biologically for teicoplanin, detailed analysis was confined to pre-dose data.[11,12]

Mean pre-dose serum concentrations were calculated for every patient over the first 3 days, from day 4 to day 7, from day 4 to the end of treatment and over the whole treatment period. Apart from the last of these periods (the whole treatment period) some patients were excluded from each mean value because they had no pre-dose measurements taken during the particular time period. In particular, some patients had measurements taken only during the first 3 days and none subsequently. For this reason, in the logistic regression the mean serum concentration over the period from day 4 to the end of treatment was used for all patients who had at least one value in this time period, but so as not to reduce the number of eligible patients, day 1 to day 3 data have been included for those patients who had no serum concentration assays after day 3. Four of the 11 patients who failed therapy had no trough concentration after day 4, whereas 12 of the 69 cured had no trough concentration after day 4.

Descriptive statistical analysis

The cured and failed groups were compared for baseline and demographic characteristics using a χ^2 or Student's *t*-test as appropriate.

Logistic regression

Logistic regression (PROC LOGISTIC, SAS 6.11, SAS Institute, Inc., Cary, NC, USA) was used to determine which variable(s) influenced clinical outcome. Stepwise selection was used to decrease the number of variables influencing outcome, with entry to the model set at 0.25 and removal from the model set at 0.3. Broadening these criteria made no difference to the results obtained.

Percentage success rate was calculated by

$$e^x/(1 + e^x) \times 100 = \%\ \text{success rate} \qquad (1)$$

where

$$x = \text{intercept} + (\text{parameter estimate}_1 \times \text{variable}_1) + (\text{parameter estimate}_n \times \text{variable}_n)$$

and $e = 2.718282$.

Variables analysed were age, body weight, mean pre-dose serum concentration, mean dose (mg or mg/kg body

weight), use of loading dose, combination versus monotherapy and MIC. Clinical outcomes classified as 'improvement' were not considered in this analysis; the only clinical categories used were cure or failure because these were considered to be definite categories. For variables for which a patient had no value, the patient was rejected from that analysis completely. Within the stepwise analysis, variables that did not contribute, or that reduced the fit of the model, were removed from the model statement sequentially. Consequently, as variables were rejected, the number of patients contributing to the model, and therefore the significance of the model, increased. Eventually two variables remained with good levels of statistical significance and a satisfactory fit.

Goodness of fit of the model was assessed using the Hosmer & Lemeshow test,[14] which compares actual with predicted frequencies of 'success' or 'failure' and provides an overall statistic for goodness of fit.

Results

Descriptive analysis

A descriptive summary of the statistical values for the variables included in the logistic regression analysis are shown in Table I.

The mean age of those cured (51 years) was lower than that of those who failed (62 years), who also tended to be of lower weight. Pre-dose serum concentrations, mean daily dose (mg/day) and mean dose (mg/kg/day) were all higher in the cured group compared with those who failed. The 95% confidence intervals for the differences observed between the means of the groups in Table I were 0.242–0.839 for age and 1.387–11.39 for pre-dose concentration. The mean pre-dose serum concentration and mean daily dose were significantly greater in those cured compared with those who failed ($P < 0.05$). Duration of treatment was substantially shorter in the failure group than in successfully treated patients. As this could equally be the result or cause of treatment failure, cumulative dose was not used in subsequent analysis (data not shown). During treatment 47 patients received teicoplanin alone, whereas 33 received combination therapy (Table I). The antibiotics used were: amikacin (10 patients), ceftazidime (six patients), rifampicin (three patients), netilmicin (three patients); azlocillin, cefotaxime, gentamicin, mezlocillin, pefloxacin and spiramycin each used in a single patient. Five patients, all in the cured group, received multiple drugs, which were unspecified in the database. The proportion of monotherapy and combination patients was similar between the cure and failure groups. All the isolates treated had teicoplanin MICs of ≤2 mg/L; however, MICs in general tended to be higher in the group cured compared with those who failed therapy (Table I).

Logistic regression

Of the variables analysed—age, body weight, mean pre-dose serum concentration, mean dose (mg or mg/kg body weight) and combination versus monotherapy—only two correlated with clinical outcome at a significance level better than 0.05. These were age ($P = 0.012$) and mean pre-dose serum concentration ($P = 0.010$) (Table II). The R^2 value for the analysis was 0.31. In a 'jackknife test' using 0.8 as a cut-off point, 52 of 67 successfully treated patients and eight of 11 treatment failures were correctly classified. This gives a sensitivity of 77.6% to identify successfully treated patients and a specificity of 72.7% to identify treatment failures. The false positive rate (patients wrongly classified as treatment success) was 5.5%. However, the false negative rate was 65.2% because 15 patients who were classified as treatment failures were successfully treated. The relationship between age, pre-dose serum concentration and clinical outcome are displayed graphically in the Figure.

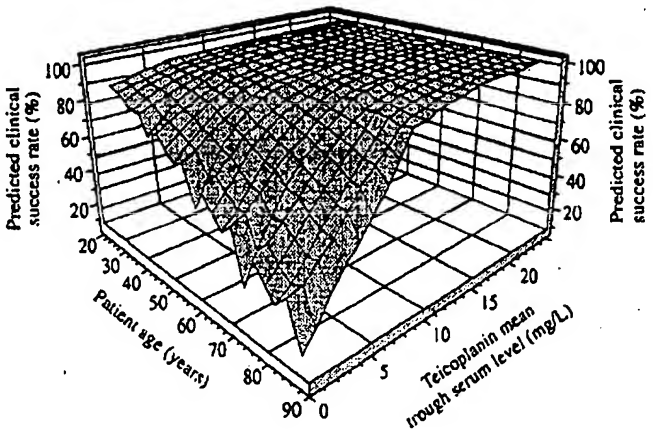

Figure. Logistic regression predictive model of clinical outcome in *S. aureus* septicaemia treated with teicoplanin.

Table I. Patient data included in logistic regression analysis

Patient population	Cured (n = 69)	Failure (n = 11)
Age (years)		
mean (S.D.)	49.4 (19.7)	61.0 (17.6)
median	51	62
range	18.0–83.0	23.0–91.0
n	69	11
Weight (kg)		
mean (S.D.)	68.1 (15.0)	63.5 (12.1)
median	66.5	60
range	38.0–103.0	45.0–85.0
n	64	11
Mean pre-dose serum concentration (mg/L)		
mean (S.D.)	7.8 (4.8)	4.4 (2.0)
median	7	3.9
range	0.3–22.0	1.5–7.6
n	64	11
Mean daily dose (mg)		
mean (S.D.)	387.6 (145.6)	286.7 (78.5)
median	400	275
range	123.8–800.0	202.9–400.0
n	69	11
Mean dose (mg/kg)		
mean (S.D.)	5.9 (2.0)	4.7 (1.8)
median	6.1	4.2
range	1.6–10.3	2.7–8.2
n	64	11
Frequency of combination therapy		
combined	29 (42.0%)	4 (36.4%)
monotherapy	40 (58.0%)	7 (63.6%)
n	69	11
Distribution of MIC values (cumulative percentage)		
missing	16	1
<0.03	0	2 (20)[a]
0.03–0.06	3 (6.2)[a]	2 (40)
0.06–0.12	4 (14.6)	1 (50)
0.12–0.25	10 (35.4)	3 (80)
0.25–0.5	17 (70.8)	2 (100)
0.5–1	9 (89.6)	0
1–2	5 (100)	0

[a]Cumulative percentage.

Worked examples

To calculate the predicted success rate for a patient aged 25 with a mean pre-dose serum concentration of 6.0 mg/L teicoplanin, we calculate x by substituting from the parameter estimate (PE) column (Table II):

$$x = \text{intercept}_{PE} + (\text{age}_{PE} \times \text{age}) + (\text{concentration}_{PE} \times \text{concentration})$$

i.e. $x = 3.3280 + (-0.0687 \times 25) + (0.4056 \times 6.0) = 4.0441$

Substituting in equation (1)

$$e^{4.0441}/(1 + e^{4.0441}) \times 100 = 98\% \text{ success}$$

Similarly, to calculate the predicted success rate for a patient aged 85 with a mean trough serum concentration of 6.0,

$$x = 3.3280 + (-0.0687 \times 85) + (0.4056 \times 6.0) = -0.0779$$

$$e^{-0.0779}/(1 + e^{-0.0779}) \times 100 = 48\% \text{ success}$$

Table II. Summary of logistic regression analysis

Variable	Degree of freedom	Parameter estimate	Standard error	Wald χ^2	χ^2 *P* value	Standardized estimate	Odds Ratio
Intercept (I)	1	3.3280	1.4146	5.5349	0.0186		
Age (*A*)	1	–0.0687	0.0273	6.3333	0.0118	–0.758552	0.934
Mean trough (*T*)	1	0.4056	0.1577	6.6114	0.0101	1.041532	1.500

Per cent success = $e^x/(1 + e^x) \times 100$, where $x = PE_I + (PE_A \times A) + (PE_T \times T)$.

From this model it is clear that the probability of successful treatment increases with mean trough serum concentration, and decreases with age.

Other variables

In a separate preliminary logistic analysis, distribution of MIC was identified as a paradoxical factor with a negative parameter estimate and with a significance level of less than 0.05. Distribution of MIC was therefore not included in overall or further logistic regression, as its inclusion masked other, more important effects.

Discussion

The pharmacodynamics of the glycopeptides teicoplanin and vancomycin are reasonably well known. It is clear that vancomycin and teicoplanin do not show concentration-dependent killing across the range of concentrations likely to be observed in human dosing.[15–17] In addition, using *in vitro* pharmacodynamic models of infection it has been shown that vancomycin simulations with maximum concentrations of 48 mg/L are no more effective than those with steady-state concentration of 8 mg/L.[18] Both teicoplanin and vancomycin have a post-antibiotic effect (PAE) against *S. aureus*, which has been found by viable count methods to be in the range 0.2–0.7 h after exposure to 5 mg/L for 1 h and 0.6–2.0 h after exposure to 25 mg/L.[19] A PAE has also been observed in a model of neutropenic thigh infection caused by *S. aureus*.[20]

Animal models using teicoplanin to treat rabbit infective endocarditis caused by *S. aureus* indicated that 4.5 mg/kg/24 h was less effective at sterilizing vegetation and reducing viable counts/g vegetation than 4.5 mg/kg/16 h. The 16 h dosing regimen produced higher extravascular teicoplanin concentrations than the 24 h schedule but animals that received the 16 h dosing regimen received a higher total dosage of teicoplanin over the 80 h of therapy than those receiving 24 h dosing. Nevertheless, these data indicate that more frequent dosing of teicoplanin may be optimal.[11] In addition, a further study in rabbit infective endocarditis indicated that 36 mg/kg/day teicoplanin administered intramuscularly was more effective in reducing the proportion of animals infected and the mean colony counts per vegetation than the same dose given intravenously. The iv dose produced 2 h and 12 h post-dose concentrations of 168 ± 28 mg/L and 26 ± 11 mg/L, respectively, compared with 68 ± 14 mg/L and 34 ± 10 mg/L after im dosing. The serum concentrations of the animals at culling were 11 ± 9 mg/L in those treated intravenously and 16 ± 11 mg/L in those treated intramuscularly; the mean teicoplanin concentrations in the vegetation were more than twice as high in the im group as the iv group.[12] These data would indicate that transient high peak serum concentrations of teicoplanin are not likely to be of benefit in killing bacteria or curing infection and that sustained concentrations over the MIC will be of benefit in terms of improving extravascular drug penetration and cure rates. Caution must be exercised, however, as there are no high-quality dose escalation or fractionation studies in either *in vitro* models of infection or animals to inform decisions about teicoplanin dosage.

We reported previously a descriptive statistical analysis of 42 cases of staphylococcal infection from the literature in which the clinical site of infection, species isolated, maintenance dose, MIC for the pathogen, pre- and/or post-dose teicoplanin concentration and clinical outcome (cure, fail, interminate) were given.[13] Dose, MIC or site of infection were not predictive of failure but only 20% of patients were cured if trough concentrations were <5 mg/L compared with 90% if they were >25 mg/L. Similarly, for post-dose concentrations, concentrations of <12.5 mg/L were associated with only a 10% cure rate, whereas ≥80% of patients were cured if the post-dose concentrations were >47 mg/L. Trough concentrations of >20 mg/L were associated with a favourable outcome. Clearly, this study had numerous methodological problems: its retrospective nature; derivation of data from six separate studies; possible variation in definition of clinical cure and timings of serum concentrations; and a relatively heterogeneous range of conditions treated. Furthermore, in many patients surgery would have had a major impact on outcome; for example, in those patients with osteomyelitis, infective endocarditis and abscesses. It was not possible to control for these.[13]

The present study corrects some of these problems. The patients were all known to have primary *S. aureus* septicaemia and hence surgery would not have influenced outcome. As the patients were recruited into clinical studies,

data collection was relatively uniform and more data were available than in the case series we analysed previously. For the treatment of septicaemia with teicoplanin, our analysis shows that the two most readily quantifiable factors that influence successful outcome are mean pre-dose serum concentration and patient age. The probability of successful treatment increases with pre-dose serum concentration and decreases with age. It appears that predicted clinical success follows a saturable kinetic pattern; for example, for those over 80 years old, clinical cures increase from <30% with trough concentrations of <5 mg/L to >90% with troughs of >10 mg/L (Figure). However, the maximum trough concentration in this study was only 22 mg/L and the vast majority were <15 mg/L, hence we cannot exclude that concentrations of >20 mg/L may not add further benefit. Indeed, in the only prospective analysis of the effect of serum teicoplanin concentrations on clinical outcome (protocol 102-013) it was shown that in the treatment of staphylococcal infective endocarditis in man, 6/10 patients failed if trough concentrations were <20 mg/L compared with 1/11 if the trough was >20 mg/L ($P = 0.04$, Fisher's Exact test).[21]

Theoretically, having decided what is an 'acceptable' probability of success, the model developed here can be used to predict what trough serum concentrations are needed for efficacy. For example, for an 85-year-old patient to have a 95% chance of success, the model predicts that a mean trough serum concentration of 13.5 mg/L would be required. Clearly, however, at this preliminary stage, such an approach must be entertained with caution. The general principle is that troughs should exceed 10 mg/L, particularly in the elderly, for infection caused by *S. aureus* (Figure).

Although an R^2 value of 0.31 (indicating that 31% of the variability in outcome is explained by the model) is statistically acceptable in an analysis of real patient data, clearly other factors still account for a substantial degree of variation and the 'jackknife test' indicates that the present model will overestimate treatment failures. The intercept term is high, as many patients' infections will resolve without treatment. We accept that factors such as co-morbidity probably play a more important role in outcome than teicoplanin serum concentrations, but the original trial data did not allow this information to be included. Only prospective trials can validate our model.

The negative correlation for distribution of MIC and successful outcome was unexpected, as it suggests that patients have a better chance of being cured if they are infected with a isolate for which the MIC is higher. Clearly, this is a nonsense, and may be explained by the skewed MIC distribution and lack of resistant isolates (MIC > 4 mg/L), which contributed to the model.

Although these data indicate that pre-dose serum concentrations are useful in predicting clinical outcome, this does not imply that all patients with *S. aureus* septicaemia require therapeutic drug monitoring. It is known that standard doses of 400 mg teicoplanin at times 0, 12 h and 24 h subsequently often produce serum concentrations of <10 mg/L.[8,22] Additional doses at 36 h or use of higher doses, say 600 or 800 mg, will result in higher trough concentrations but will increase drug acquisition costs. To recommend therapeutic drug monitoring of all patients routinely receiving teicoplanin for *S. aureus* septicaemia, randomized prospective studies would have to be performed to confirm the benefits in terms of increased efficacy or reduced cost, compared with just using larger doses. Failure to do this will repeat the mistakes that occurred with vancomycin monitoring.[23]

In conclusion, these data confirm that pre-dose serum concentrations are a major predictor of outcome in conjunction with patient age; however, a single model based on these two factors still leaves much of the variability in outcome unexplained.

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